(a) introducing a liquid containing said macromolecule into a microchannel containing a membrane;

(b) electrokinetically collecting said macromolecule on said membrane; and

(c) analyzing the macromolecule collected on said membrane, or after removing said macromolecule from said membrane by applying either a pressure gradient or voltage across said membrane to affect said removing.

REMARKS

Claims 13-29 were rejected under § 112, 1st ¶ for lack of an enabling disclosure.

Claims 18 and 19 remain rejected under § 112, 1st ¶, for not being adequately supported by the written description of the specification.

Claims 13-29 were rejected under § 112, 2nd ¶, for indefiniteness.

Claims 13-29 were rejected under § 102(b) as being anticipated by Tomlinson et al. ("Tomlinson). Claim 13 and 29 were amended to recite additional limitations that are not taught by Tomlinson. Accordingly, Tomlinson does not anticipate the Applicants' claims.

The specification has been amended by a replacement page that includes the generic designation of the detergent NP-40.

The title and claims were amended as described above. In view of these amendments and the remarks herein, Applicants request withdrawal of all rejections.

Applicants' Invention

The Applicants' claims relate to a method of isolating macromolecules based on their migration through a buffered solution, wherein an electric field (i.e., potential difference) is applied across said solution. This is achieved in part, by injecting the macromolecules to be isolated into a microchannel. The microchannel is functionally, a tube or conduit that is open on both ends where it contacts the reservoirs of buffered solutions. Thus, when a potential difference is established between the two reservoirs, the microchannel becomes the conduit of the current – ions and the charged macromolecules will migrate in one direction .

Accompanying the method claims are claims directed toward an apparatus for practicing the method. A key feature of the apparatus is that within the microchannel's lumen is inserted a porous membrane . By choosing a membrane having specific properties (e.g., size of pores or net positive or negative charge, degree of inertness) the membrane permits ions to flow through the pores, while the macromolecule is collected on the membrane surface.

Once collected on the membrane, two basic approaches for retrieving the macromolecule may be used: (1) disassemble the apparatus as shown in Figure 6, remove the membrane and use the membrane with the macromolecular sample upon it for subsequent analyses; or (2) reverse polarity, and elute the macromolecules off the filter, and through the microchannel and collect them in a manner reminiscent of collecting column fractions, as in Figures 4 and 5.

The isolated macromolecules are then available for any type of analysis known to those with skill in the art that are typical of macromolecules present in solution or trapped on a filter. Because these methods of analysis are known to those in the art, they are not described in detail in the claims.

Applicants' Disclosure Clearly Satisfies the Enablement Requirement as Provided in MPEP § 2164

In order to make a rejection for nonenablement, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for in the specification. MPEP § 2164.04. In addition, the PTO guidelines require that

> a specification disclosure which contains a teaching of the manner and process of making and using an invention in terms corresponding in scope to those used in describing and defining the subject matter...must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. (Emphasis added).

The Applicants respectfully suggest that the Examiner has not met this burden because in view of Applicants' highly detailed teachings, the Examiner has not indicated a reasonable basis for doubting one or more of the objective truths contained in the specification, as is required by the PTO guidelines. Id., citing In re Marzocchi, 439 F. 2d, 220,224 (CCPA 1971).

Instead, the Examiner provides only conclusory statements as to, *inter alia*, the need of one with skill in the art to perform undue experimentation because of insufficientf guidance. See Office Action page 2, line 10 to page 3, line 5-6. Such statements do not satisfy the PTO's standard for maintaining a rejection, i.e., that of "making specific findings of fact, supported by evidence...." MPEP § 2164.04, page 2100-179, 2nd¶. Accordingly, the rejection under § 112 for nonenablement should be withdrawn. However, in support of withdrawal of the rejection, the Applicants address the Examiner's comments in turn.

Quantity of Experimentation Needed

The Examiner's conclusion on page 3, lines 11-12, by itself cannot be viewed as more than an unsupported conclusory statement. The specification describes in laboratory-manual style and detail the preparation of samples and

the appropriate buffers to use with (a) nucleic acids, pages 9-12; (b) viruses pages 12-14; (c) proteins pages 14-16; and (d)bacteria, pages 16-17. It is known in the art that sample preparation is one of the key parameters to consider when designing methods to isolate macromolecules. It is only required that sufficient guidance to practice the invention be disclosed – it is not necessary to provide support for every permutation of the claimed method.

Further, there are also the Examples on pages 20-25.

This disclosure describes *inter alia*:

- the nature of the apparatus, and the microchannel;
- materials useful for constructing and coating translucent microchannels;
- examples of buffers to be used, and the appropriate pHs;
- the types of different buffering compounds and salt concentrations;
- the nature of the sample buffer so as to impart the proper net charge on the macromolecule or particle to be isolated;
- suggestions of different dyes with which to label the macromolecules of interest;
- the types of filters and the approximate pore diameter of filters to be used with the different macromolecules to be isolated;
- how to lyse filter entrapped virus and bacteria;
- when it would be useful to reverse the voltage in elution procedures;
- suggestions for which post-isolation analysis may be useful;
- adaptations for combining with immunological methods and fluorescent methods;
- Derivatization of nucleic acids and viruses for electron microsco;y;
- Examples of voltages to apply, and for a particular length of time.

This disclosure is clearly sufficient to enable one with ordinary skill in the art to practice the invention with respect to proteins, nucleic acids, virus and bacteria. One with ordinary skill, such as those on par with a doctorate in biophysics or biochemistry, would have no problem making any trivial

adjustments, e.g., pH, buffer, voltage, membrane type, in order to adapt the invention for other macromolecules.

The Examiner has not provided any reasonable explanation or finding of fact to support the position that the disclosure is non-enabling. Accordingly, it is respectfully requested that this ground of rejection be withdrawn.

Amount of Direction or Guidance

The Examiner's reliance solely on Applicants' Examples on page 20 to 25 to evaluate whether the disclosure is enabling does not fairly represent the sum of Applicants' teachings. In support of this conclusion, Applicants note Examiner's comment on page 4, lines 5-6, that there is not "enabling guidance for the analysis of any molecules other than the isolated plasmid DNA used in the above-identified examples." This is most certainly inaccurate.

The Applicants direct Examiner's attention to pages 12-20, wherein Applicant describes in detail reminiscent of undergraduate level laboratory manuals, the sample preparations of virus, protein and bacteria specimens for use with the claimed method. Numerous variations are presented. Further included are discussions relating to the appropriate pH/buffer/charge conditions to use. One with skill in the art would clearly understand from this disclosure how to prepare any of the disclosed macromolecules for use with the claimed method and to isolate and analyze said macromolecule. There is no reasonable basis or finding of fact to support the notion that one with ordinary skill would require undue experimentation to practice the method within the scope of the claims. Accordingly, this ground of rejection should be withdrawn.

Nature of Invention

The Examiner erroneously concludes that the invention relates to physiology and chemistry. This conclusion is then used as a platform to invoke

In re Fisher for the proposition that this invention requires a greater level of enablement due to the unpredictability of the art. The Applicants' are confused and respectfully request clarification as to the basis of this conclusion.

Perhaps the Examiner sees the use of bacteria and virus as expanding the scope of the invention to physiology, but this is improper. **There is nothing in the specification that connects the invention to any physiological process or measurement thereof**. The invention relates to isolating macromolecules including intact viruses or bacteria based on their sizes, shapes and net charges. ***There is not even one connection, suggestion or teaching to link the invention to physiology***.

The Applicants respectfully request that the Examiner specifically indicate the physiological nature of the claimed methods so Applicants' may address the matter more concretely.

Further, the Examiner simply misapplies *In re Fisher,* which dealt with the ***unpredictability of chemical reactions***. ***There are no chemical reactions being claimed***. Nor is there a chemical reaction included as an indispensable element of any of the claims. The invention relates to separating molecules based on their physical attributes – size, shape, net charge and charge density. The fact that molecules are involved does not in any way support the Examiner's view that the invention is based on chemical reactions, and therefore comes under *In re Fisher*.

The invention does not require any starting materials, intermediates or products, as these terms are used in chemistry. The macromolecules as used herein do not catalyze reactions, nor are they converted during their isolation to other molecular species — they are merely being separated in a highly sensitive and novel manner. Moreover, the physical laws governing electrophoresis have been known since the 1960s, and are well understood by those with skill in the art, and are not unpredictable.

In sum, the Examiner has improperly characterized the nature of the invention, and incorrectly categorized the art as unpredictable. There has been no reasonable explanation nor finding of fact to support the conclusion that the claimed subject matter constitutes unpredictable subject matter. Accordingly, under PTO guidelines this ground of rejection should be withdrawn.

State of the Prior Art

The meaning of the Examiner's opening paragraph in this section is unclear. The claimed invention has nothing to do with chromatography, and large-scale gel electrophoresis of proteins and nucleic acids. On the contrary, the invention is directed to very small-scale electrophoresis. Small enough, in fact, to be useful in chip technology. See top of page 5. Thus, the Applicants respectfully suggest that the Examiner's perception of the state of the art is apparently based on the wrong art.

Further, Examiner's statement that analyzing "all types of macromolecules" via the claimed invention "is far from routine" is at least partially correct. This is why Applicants maintain the position that their claimed method is novel and nonobvious.

However, as an assessment of the art which supports a finding of nonenablement, the Applicants are not in agreement. If the Applicants assume *arguendo*, that the Examiner is suggesting that because the method is not routine that Applicants must supply further disclosure, the Applicants strongly disagree. Pages 9-25 of the specification are completely devoted to illustrating the various aspects of carrying out the invention, and does so in minute detail. All that is required is that one of ordinary skill in the art be enabled to practice the claimed method. It is clear that an artisan with a Ph.D. in biophysics or biochemistry would have no trouble practicing the invention in view of the disclosure.

It is respectfully requested that this ground of rejection be withdrawn.

Breadth and Scope of Claims

Beginning on page 5 of the Office Action, the Examiner improperly interprets the scope of the claims and then proceeds to support the rejection by asserting this improper interpretation.

There is absolutely no reasonable basis to conclude that Applicants' method encompasses "any one or combination of analytical methods on virtually [any] compound or composition of matter."

The preamble of the amended claim clearly indicates that the invention as described is a method that is largely directed to the isolation of macromolecules. The invention is not directed to specific analyses, as the Examiner seems to suggest. A claim limitation reciting "thereafter analyzing the macromolecules" is clearly within the scope of the claims. This is because one with skill in the art would know what analyses can be performed on filter-concentrated specimens, and thus would know when using the method is appropriate. The claims clearly do not cover virtually any analytic method, and the Examiner has improperly read this limitation into the claim. The limitation is merely the act of analyzing the isolated macromolecule according to methods known in the art.

The Examiner improperly read another limitation into the claim. A plain reading of claim 14 clearly identifies nucleic acids, viruses, proteins, bacteria or fungi. It is not reasonable to interpret this limitation as covering "any composition of matter, organic in nature or otherwise." The Examiner has provided no line of reasoning or finding of fact to support imposing this overly broad and scientifically incorrect interpretation of the claim.

Throughout the Office Action the Examiner relies on the absolutely irrelevant point that that bacteria or fungi are "life forms." Indeed they are, but the method is not directed to any issue relating to live microbes or microbial functions. In fact, the claimed invention works just as well if the microbes were dead. It must be understood that the invention is directed to exploiting the size, shape and net charge on the surface of these microorganisms to facilitate their isolation. Their viral, bacterial or fungal nature is completely irrelevant .

In fact, the proteins, lipids and sugars on the surfaces of the virus and bacteria that impart upon them their characteristic net charges are also functionally irrelevant with respect to the isolation method. It is not what functional properties these macromolecules have, but only their charges.

If the surface proteins of bacterial or fungal cells were extracted and incorporated into lipid vesicles (i.e., liposomes), the claimed invention could still be practiced to concentrate the protein-containing liposomes on the membrane insert. This is because the bacterial, viral or fungal nature of the particle being concentrated is irrelevant. Thus, it is improper to assess this application by imposing a physiological slant on it.

On page 5, 3rd ¶, the Examiner reasserts the undue experimentation argument. The Examiner states that in order to practice the invention a skilled artisan would have to determine parameters such as: how to manufacture the devices having "***any*** number of microchannels of ***virtually any*** diameter..." including where the "substrate ***is not translucent*** and where the microchannels ***may comprise branch points***." The Examiner again improperly imposes an overly broad scope on the claimed invention to maintain his rejection.

In response, the Applicants point the Examiner's hypotheticals are improper, in as much as they represent embodiments that are highly unlikely to arise. For example, there is no foreseeable value in a capillary that is not

translucent and thus, amenable to analysis by UV. Further, there are ample teachings relating to the structure of the apparatus. These teachings are sufficient, to enable one with ordinary skill to practice the invention. For example:

- The apparatuses used by Applicants were purchased from Hewlett-Packard (Tables 1-2) or Beckman (Table 3), and is known to those with skill in the art. Thus, there is no need to construct from scratch, the device of the invention.
- The diameter of microchannels are disclosed in each of Tables 1-3, and vary from 50 μm to 75 μm. On page 6, lines 11-12 give the suggested dimensions of the microchannel, as well as the materials it is made from.
- On page 6, 14-17, the disclosed materials for constructing microchannels are transparent. The channels are disclosed as being "ideally" transparent. Similarly, transparent, chemically inert coatings are suggested. If one with skill prefers to use a microchannel that is not translucent (as in Examiner's hypothetical), **then he or she is not using the apparatus within the scope of the teachings.** It is improper to reject a claim based on this unlikely modification. Choosing an opaque microchannel is highly unlikely because it precludes detecting the macromolecules of interest – i.e., UV light is the most convenient method to monitor macromolecules (proteins, nucleic acid absorb UV) or virus and bacteria (by light scattering; i.e., turbidity).
- It is widely known in the art that substrates or compartments comprising the apparatus will be chemically inert and thus not "react with components of the macromolecule." Office Action, page 5, middle 3rd ¶. The number of commercially available electrophoresis apparatuses made of inert plastics is very large. In fact, it is unlikely that one could purchase a unit that does chemically react with macromolecules. Nonetheless, such a use is beyond the suggested teachings.
- One with skill in the art can readily determine how many microchannels and how many branch points without undue experimentation. It is likely,

given the sample size of macromolecules to be separated, that this can be determined with no experimentation whatsoever. For example, on page 20, lines 16-17, the invention teaches its use across a broad range of nucleic acid concentrations. Specific values are given in the 2nd ¶.

In sum, the Examiner has indicated some of the variables to consider in practicing the invention. However, it is respectfully suggested that he also improperly exaggerates the difficulty that one with skill in the art would have in practicing the invention.

Beginning on page 3, 4th ¶, the Examiner reasserts that no examples were given other than plasmid DNA. The Applicants respectfully disagree.

On page 24, the section *Coupling with electron microscopy* provides an example of using Herpes Simplex virus (HSV-2). The parameters in Table 3 were used. Also provided is the amount of virus used; conditions for fluorescent labeling with YOYO to detect the sample's position in the microchannel. The virus was successfully isolated and visualized by negative stain electron microscopy. There is no reason why the exact same protocol would not work for any virus or bacteria.

As stated above, most of the technical differences between the types of samples used will manifest itself in the sample preparation, prior to the electrokinetic analysis. Pages 9-19 provide very detailed disclosures of how either proteins, nucleic acids, virus or bacteria may be prepared.

In sum, **the Examiner's conclusion that "no other compound or macromolecule...has [been] exemplified" is simply inaccurate**. Accordingly, it is respectfully requested that this ground of rejection be withdrawn.

On page 6, the Examiner claims that "the disclosure does not set forth a reproducible method whereby any membrane can be inserted into a microchannel...." This is incorrect. The Examiner's attention is drawn to Figures 6 and 7, and the relevant text on page 8, lines 14-31. Herein, the device is disclosed as being separable into two parts, which are reassembled with a porous membrane in between. One would have virtually no trouble understanding this design. Thus, the Examiner's statement that the specification is silent "on how to extricate the micromembrane from the microchannels" is incorrect. In fact, based on the drawings in Figures 6 and 7, it is shown to be a trivial issue, and cannot reasonably support the instant rejection.

Further it is known by those in the art that the binding properties of filters depend on how the filter is made. In the present application, molecules, virus and bacteria are being concentrated on a filter based on size and charge. It is widely known that inert filters having calibrated molecular weight cut offs, or known pore diameters can be purchased from several sources, e.g., Millipore, Costar, Nunc, etc. Even if they did not know this beforehand, one with skill can easily find these components in the appropriate catalogs.

The Examiner states that there is "not set forth a reproducible procedure whereby an electrokinetic force would be applied when the device is void of any means to provide for such." The claims are directed to a method, and the device referred to in claims 18-19 and 24 represents only that part of the apparatus that relates to the inventive aspect of the method. The device need not refer to elements already well-known to those with skill in the art.

Further, it is disclosed in Figures 1-5 and 8 that the electrokinetic force may be produced by a voltage supply or a pressure differential placed across the membrane. It is well known in the art to create voltage or pressure differentials, to affect the movement of charged particles. Further, this force is not part of the claimed invention, and therefore does need to be recited in the claims.

In view of these teachings, it is clear that the same principle will also work for one microchannel as for the 400 recited in claim 18. There need be only a scaling up of the method. The creation of DNA microchips is an evolving and well-known technology. There is no reason whatsoever to conclude that the claimed invention cannot be adapted for such a purpose. Nor does the Examiner provide a line of reasoning or finding of fact supporting his conclusion.

On page 7, 2nd ¶, the Examiner asserts that the device and method claims do not recite any analytical steps and methods correlated with <u>any results obtained</u>. <u>This assertion is incorrect because there are several results directed to characterizing the use of the invention</u>. For example:

- Page 22, 2nd ¶. Applicants provide results demonstrating that their method can be used to concentrate three different DNA samples on the filter, and quantitatively recover said DNAs by reversing the polarity. Therefore, immobilized molecules can be retrieved from the membrane without appreciable losses.
- Page 23, ¶¶ 1-2. Applicants demonstrate the injection of low levels YOYO-labeled DNA, to show that even very small amounts in a sample can be quantitatively injected into the microchannel, and can be concentrated <u>1000-fold</u>. See page 24, lines 1-2.
- Page 24. Applicants demonstrate that DNA can be concentrated on the membrane, and then be derivatized with YOYO. Thus, prelabeling need not be performed.
- Page 24, 3rd and 4th ¶¶. The same procedures can be used for labeling HSV with YOYO. The viruses were concentrated and eluted by reverse polarity, and the progress followed by measuring fluorescence.
- Page 25, 1st ¶. The HSV was placed on electron microscopy grids, negatively stained, and their presence and structure determined. Applicants also disclose that this was the first time that viruses were subjected to such treatment.

- Figure 4 schematically represents the behavior of macromolecules in the microchannel, and how fluorescence measurements aid in following the process. The Applicants indicate on pages 11, 14, 16 and 17 respectively, that nucleic acids, virus, protein and bacteria can all be analyzed using similar techniques. It is known to those with ordinary skill that the progress of certain isolation procedures involving nucleic acids, proteins, viruses and bacteria may be followed by UV absorption, light scattering, or fluorimetry.
- Various explanations throughout these pages provide additional guidance for using the method.

Conclusion of the Response to the Nonenablement Rejection

The test of enablement is whether one skilled in the art can use the disclosure, coupled with information known in the art, to practice the invention without undue experimentation. MPEP §§ 2164. 2164.01. Accordingly, a patent "need not teach, and preferably omits what is well-known in the art." Id., *citing* In re Buchner, 929 F. 2d 660, 661 (Fed. Cir. 1991). In fact, even if the specification lacks any working examples or evidence that the claimed invention works, that is not sufficient, by itself, to reject the claims. MPEP § 2164.02, at 2100-177. However, as detailed in the foregoing discussion several examples and results have been provided.

It is respectfully suggested that the Examiner has not adhered to the PTO's expression of the enablement requirement, but has instead substituted his own understanding for that of the skilled artisan. For example, the Examiner stated the belief that the claimed invention related to physiological issues. Based on this conclusion he improperly rendered the art of this application as "unpredictable." This is not a proper basis for maintaining the rejection.

Predictability in an art arises when one with skill in the art can readily anticipate the effect of a change within the subject matter of the

invention. MPEP § 2164.04. In Applicants' invention, any changes in size or charge of the macromolecule can be predictably compensated for by merely providing a higher/lower voltage, or a membrane with larger/smaller pore diameter, or a different buffering system. If the skilled artisan uses a dye different from YOYO, the proper conditions would be predictable because the dye's product data always provides the correct wavelengths of use. Alternatively, one with skill can themselves determine the optimal wavelength within one hour.

Further, this same predictability militates in favor of finding that undue experimentation would not be required to practice the invention. The variables that may require optimizing include pH, buffer type, dye type, amount of sample, size of voltage drop, etc. These types of manipulations are routinely performed in a laboratory when approaching a new experiment. In view of Applicants' teachings, it is not likely that one with skill would require any experimentation to practice the invention.

Last, even if the nature of the experimentation were complex this does not automatically amount to undue experimentation. MPEP § 2164.01, *Undue Experimentation*. However, in the instant invention, the nature of the experimentation is trivial and is routinely performed by those in the art. Accordingly, the invention would not require undue experimentation to be practiced.

In other instances it appeared that the Examiner expanded the scope of the invention, and then rejected the claim based on that expansion. See page 5, *et seq*. For example, it is simply unreasonable to conclude that claim 14's reciting of nucleic acid, protein, virus, bacteria and fungus is indicative of the Applicant covering virtually every type of composition, organic or otherwise. The Examiner did not provide any facts, or a line of reasoning to reach that conclusion as required. MPEP § 2164.04.

Finally, the Applicants direct the Examiner's attention to the numerous instances in the Office Action, wherein he asserted that the specification was devoid of specific types of teachings and results, when in fact there was an **abundance** of technical guidance and experimental results. It appeared that, perhaps, the Examiner had a different view of what constitutes proper guidance and results. However, it is in reference to one with skill in the art that these teachings must be evaluated. Accordingly, the specification was clearly enabling to the ordinary skilled artisan.

The Applicants remind the Examiner that In rebutting the Examiner's remarks, the Applicant's arguments and evidence "need not be conclusive, but merely convincing to one skilled in the art." MPEP § 2164.05. (Emphasis in original). It is also PTO policy that when a patentability decision can reasonably be viethe Applicantsd as going either way, the proper outcome is to decide for the applicant. In view of this discussion, it is respectfully requested that the rejection for lack of enabling disclosure be withdrawn.

Claims 18 and 19 are Adequately Supported by the Specification

"To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." MPEP § 2163 (I). It is respectfully suggested that the Examiner has substituted his own perspective for that of the ordinary skilled artisan.

The Examiner rejects claim 18 for several reasons. Each reason will be addressed in turn.

It is alleged that the specification fails to set forth a device permitting "any form of analysis...all possible macromolecules." This ground for

rejection is ambiguous because the invention does not suggest anywhere that it can be used for "any form of analysis." Office Action, page 9, 2nd ¶.

What the Examiner seems to be saying is that he sees the claims as trying to cover all subsequent methods of analysis *per se*. This is not a reasonable reading of the claims. The claims only say that if a sample is prepared by the claimed method, and analyzed, it reads on claim 13 because of the use of the claimed method. It is the act of analyzing in conjunction with the steps of the method that constitute the claimed subject matter, and not any number of specific analyses.

Therefore, using any non-claimed sample preparation in conjunction with a particular standard analysis does not read on claim 13 because the claimed invention has not been used. The Applicants are not incorporating the universe of specific analyses as claim limitations, therefore it is improper to require that the specification adequately disclose all analyses and potential uses of the invention. One with skill would clearly understand this point. Examiner's reference to "any form of analysis...all possible macromolecules" does not accurately describe the scope or subject matter of the claims. It is another attempt to expand the scope of the invention, and then use this expansion as a basis of rejection.

Applicants respectfully request withdrawal of this ground of rejection.

The Examiner states that there lacks adequate support for the device in claim 18. In his *response to the prior argument* on page 10 of the Office Action, it is clear that he bases this conclusion on the incorrect dimensions of the entire module. This module Examiner referred to is shown in Figure 7, and discussed on page 8, line 30 to page 9, line 1. Hothe Applicantsver, this is not the correct embodiment.

The device in claim 18, having 1-400 microchannels, is shown in kind, in Figure 6. To exemplify the device, only 6 channels are shown. This is described on page 8, lines 14-24. As described in the legend to Figure 6, the principle of operation is the same as those exemplified for single capillary microchannels devices shown in Figures 1-5, but not Figure 7. One with skill in the art clearly understands that the adaptation from one channel to multichannel is simply one of mechanical design, not scientific principle.

The Amended Claims are not Indefinite Under § 112, 2nd ¶

Applicants' amendments to the title and the claims clarify the general nature of the invention as the Applicantsll as more clearly specify what is being claimed.

The original title "Electrokinetic Sample Preparation" accurately describes a major part of the disclosure's teachings. Hothe Applicantsver, the Examiner's comments indicate that the title does not clearly reflect claimed subject matter. In response, the title has been amended to "Electrokinetic Isolation of Macromolecules."

The new title more clearly conceptually connects the method and apparatus of the claims to the overall goal of the invention – to isolate macromolecules according to their physical characteristics, and in such a manner as to substantially maintain their structural and chemical properties.

The latter point is important, because an investigator may then use the isolated macromolecules to perform various analyses in accordance with how the molecules are finally obtained, e.g., by disassembling the apparatus and removing the macromolecule-containing membrane, or in solution by reversing the voltage and collecting fractions containing the macromolecule.

Claims 13, 20, 25, and 29 have been amended to recite "A method for isolating a macromolecule for subsequent analysis." This amendment incorporates the issues above, but also, further clarifies that the analyzing is "subsequent" to the isolation method. The amended claims cannot be considered to be omnibus claims.

It is important to emphasize that the claims do not seek to cover the analysis methods *per se*, and thus Applicant need not include the steps in the subsequent analyses. What is covered is the isolation of a macromolecule that is to be analyzed.

Although the Examiner believes this too broad, the Applicants reiterate that no specific analyses by themselves are covered. Further, because no prior art rejections the Applicantsre applied in this case, Applicant is entitled to broad claims commensurate with the new ground being covered by the invention. *See* In re Hogan, 194 527, 537 (CCPA 1977).

Claim 16 was rejected because it is allegedly confusing as to when the recited analyses are to be performed. One with skill in the art would not find this claim confusing because the claims now recite the method of isolation and subsequent analysis. Each of these terms is the name of a kind of analysis to be performed on the macromolecule after the isolation by the method claimed herein. See specification page 5, lines 23-27.

It is respectfully requested that this rejection be withdrawn.

The Examiner's rejection of claims 18-23 for omitting a "means that allow electrokinetic collection of nucleic acids on the membrane" should be withdrawn for requiring elements known to those with skill in the art. Once again, the Examiner is improperly substituting his own understanding for that of one of ordinary skill in the art. Office Action, page 12, 3rd ¶. The PTO guidelines

state that "[d]efiniteness of claim language must be analyzed, not in a vacuum, but in light of:

> (A) The content of the particular application disclosure;
>
> (B) The teachings of the prior art; and
>
> (C) The interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made."

MPEP § 2173.02.

The Examiner seems to believe that the specification did not disclose the use of voltages in these methods, and that one with skill in the art would not understand by reading the text, and figure legends, that the figures disclose a component acting as a voltage source. Further, Examiner apparently believes that neither the prior art nor one with ordinary skill would understand that electrical connections are required to separate macromolecules by electrokinetic method.

It is clear that it is well-known in the art that any molecular separation method based on differential migration of molecules within an electric field, requires the electric field. As such, the electrical connections need not be recited in the claims. This rejection would be no different than the Examiner rejecting claims for a new kind of electric shaver that did recite a power cord element. It is respectfully suggested that the Examiner withdraw the rejection.

Tomlinson Does not Anticipate Amended Claim 13

Tomlinson teaches a method of chromatographically analyzing a mixture of molecules, wherein the mixture of molecules is applied to filter membranes by applying a pressure gradient across the filter. Once loaded onto the filter, the molecules are eluted from the membrane prior to electrophoresis in methanol acetonitrile (50:50) or methanol water (80:20). The electrophoretic

separation then affords high resolution analysis of the mixture. This is different than the claimed invention.

Applicants' method does not require any solvent elution. Removal of macromolecules from filters is achieved merely by pressure or voltage. Further, Tomlinson does not provide for any sample to be analyzed while retained on the filter as does the claimed method. Thus, the claimed procedure is significantly more simple and versatile than Tomlinson's. These differences are recited in the amended claims 13 and 29.

CONDITIONAL PETITION FOR EXTENSION OF TIME

If any extension of time for this response is required, Applicants request that this be considered a petition therefore. Please chare the required fee to Deposit Account No. 14-1263.

Please charge any further insufficiency of fees, or creadit any excess to Deposit Account No. 14-1263.

CONCLUSION

Applicants have addressed each of the Examiner's comments. Amendments to the title and claims have incorporated several of Examiner's suggestions as to express the subject matter more clearly.

Further, the technological issues that Examiner has raised have been specifically addressed. Accordingly, Applicants respectfully request reconsideration of the application, and that all rejections be withdrawn.

Respectfully submitted,

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SEPARATE SHEET OF MARKED UP CLAIMS

Claim 13. (Amended) A method for ~~analyzing macromolecules~~ isolating a macromolecule for subsequent analysis, said method comprising electrokinetically collecting macromolecules on a membrane in a microchannel, and thereafter analyzing the macromolecules ~~collected~~ either while collected on said membrane, or after removing said macromolecule from said membrane by applying either a pressure gradient or voltage across said membrane to affect said removing.

Claim 20. (Amended) A method for ~~analyzing macromolecules~~ isolating a macromolecule for subsequent analysis, said method comprising providing a device according to claim 18, electrokinetically collecting macromolecules on a membrane of said device in a capillary of said device, and thereafter analyzing the macromolecules collected.

Claim 25. (Amended) A method for ~~analyzing macromolecules~~ isolating a macromolecule for subsequent analysis, said method comprising providing a device according to claim 24, electrokinetically collecting macromolecules on a membrane of said device in said channel of said device, and thereafter analyzing the macromolecules.

Claim 29. (Amended) A method for ~~analyzing macromolecules~~ isolating a macromolecule for subsequent analysis, said macromolecule being selected from the group consisting of nucleic acids, viruses, proteins, bacteria and fungi, said method comprising:

a) introducing a liquid containing said macromolecule into a microchannel containing a membrane;

b) electrokinetically collecting said macromolecule on said membrane; and

c) analyzing the macromolecule collected on said membrane, or after removing said macromolecule from said membrane by applying either a pressure gradient or voltage across said membrane to affect said removing